

Adoptive transfer of MART-1 T cell receptor transgenic lymphocytes and dendritic cell vaccination in patients with metastatic melanoma.

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Public Summary:

Purpose: It has been demonstrated that large numbers of T cells (a type of white blood cell) that target and kill tumor cells can be manufactured by genetically engineering a subject's own white blood cells. In mice, this treatment was optimized by exposing the T cells to cancer specific proteins, through a technique called dendritic cell (DC) vaccination. We have developed a method to manufacture both T cells and DCs in 1 week and have administered them together to subjects in a clinical trial. **Experimental Design:** A clinical trial was performed in which the MART-1 T cell receptor (TCR) gene was introduced into the subject's T cells. These genetically engineered T cells were administered to the subject with DCs manufactured from the subject's white blood cells that contain MART-1. The DCs containing MART-1 stimulate the T cells to be activated. T cells and DCs were manufactured in 6-7 days and were either infused fresh or were frozen. **Results:** Fourteen patients with melanoma were enrolled in the trial and 69% of those treated showed evidence of tumor regression. The number of MART-1 TCR cells in the blood was highest at approximately two weeks after being transferred into the body. The cells that were infused fresh lasted longer in the body and were more effective than those that were infused after being frozen. It was only apparent using fresh cells that the DC vaccination could further increase the number of tumor-specific T cells inside the body. **Conclusion:** The concept of using a DC vaccination with MART-1 TCR specific T cells manufactured over a 1 week period is feasible and results in antitumor activity, but improvements must be made in order to improve the efficacy of the treatment.

Scientific Abstract:

PURPOSE: It has been demonstrated that large numbers of tumor-specific T cells for adoptive cell transfer (ACT) can be manufactured by retroviral genetic engineering of autologous peripheral blood lymphocytes and expanding them over several weeks. In mouse models, this therapy is optimized when administered with dendritic cell (DC) vaccination. We developed a short one-week manufacture protocol to determine the feasibility, safety and antitumor efficacy of this double cell therapy. **EXPERIMENTAL DESIGN:** A clinical trial (NCT00910650) adoptively transferring MART-1 T cell receptor (TCR) transgenic lymphocytes together with MART-1 peptide pulsed DC vaccination in HLA-A2.1 patients with metastatic melanoma. Autologous TCR transgenic cells were manufactured in 6 to 7 days using retroviral vector gene transfer, and re-infused with (n = 10) or without (n = 3) prior cryopreservation. **RESULTS:** 14 patients with metastatic melanoma were enrolled and nine out of 13 treated patients (69%) showed evidence of tumor regression. Peripheral blood reconstitution with MART-1-specific T cells peaked within two weeks of ACT indicating rapid in vivo expansion. Administration of freshly manufactured TCR transgenic T cells resulted in a higher persistence of MART-1-specific T cells in the blood as compared to cryopreserved. Evidence that DC vaccination could cause further in vivo expansion was only observed with ACT using non-cryopreserved T cells. **CONCLUSIONS:** Double cell therapy with ACT of TCR engineered T cells with a very short ex vivo manipulation and DC vaccines is feasible and results in antitumor activity, but improvements are needed to maintain tumor responses.

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